Paternal Exposure to Methotrexate and Pregnancy Outcomes

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ABSTRACT. ***Objective.*** To assess the risk of major malformation in the case of paternal exposure to methotrexate (MTX) at the time of conception.

Methods. Using prospective data of our Teratology Information Service, we analyzed outcomes of paternal MTX exposure at the time of conception or up to 3 months before conception.

Results. We report on the outcomes of 42 pregnancies involving 40 men treated with MTX at the time of conception. Twenty-three men were treated for an inflammatory disease (54.8%), 9 for psoriasis (21.4%), and 8 for a malignant disease (19.0%). Weekly dosages varied between 7.5 mg and 30 mg. The pregnancies resulted in 36 live births, 3 spontaneous abortions, and 3 voluntary abortions. No congenital malformation was observed at birth.

Conclusion. Based on our results and case reports in literature, paternal MTX exposure at the time of conception does not seem to raise any major concern for offspring. (First Release Jan 15 2011; J Rheumatol 2011;38:628–32; doi:10.3899/jrheum.100600)

Key Indexing Terms:
PREGNANCY OUTCOME METHOTREXATE PATERNAL EXPOSURE

Methotrexate (MTX) is a folic acid antagonist, used in the treatment of some cancers, rheumatic diseases, and psoriasis. It acts as an inhibitor of tetrahydrofolate dehydrogenase and prevents the formation of tetrahydrofolate, necessary for the synthesis of thymidylate, an essential component of DNA.

The usual weekly dose of MTX varies according to indication from 7.5 to 25 mg in inflammatory diseases and to as much as 12 g/m^2 in neoplasia.

A fetal aminopterin/MTX syndrome has been described in the offspring of women taking MTX for malignancies or as an abortifacient[1]. Features of this syndrome include mainly skeletal abnormalities (involving the skull and limbs), microcephaly, and hydrocephalus[2].

While the teratogenic effects of MTX are unquestionable (i.e., when a pregnant woman is directly exposed to the drug during the first stages of pregnancy), the potential hazards for the fetus when the father is exposed to MTX at the time of conception remain unclear. Little information is available about offspring conceived under this condition. Paternal conception under MTX raises 2 types of theoretical questions: the potential genotoxic effect of MTX on sperm, leading to possible malformations, chromosomal rearrangements, or longterm diseases in children; and the ability of the amount of MTX present in the seminal fluid to induce birth defects by crossing the vaginal mucosa after sexual intercourse with a pregnant woman.

Around 20 case reports have been published concerning apparently normal children born to fathers treated with MTX at the time of conception.

Because of this small number and to contribute information for risk assessment in such circumstances, we conducted a prospective followup of pregnancies in which the father was treated with MTX at the time of conception or within the 3 months before conception (i.e., one spermatogenic cycle).

MATERIALS AND METHODS

The Paris Teratology Information Service-TIS (CRAT) is a medical counseling service, identifying risk assessment of drugs and other environmental or occupational exposures on fertility, pregnancy, and lactation[3]. Only healthcare professionals can ask for information.

All patient characteristics (disease, drug dosages, etc.) and familial history are provided by the healthcare professional. A month after the estimated date of birth, a questionnaire related to the main events during pregnancy, additional exposures, and the outcome is automatically sent to the healthcare professional. All information concerning pregnancy outcomes is medically confirmed by the healthcare professional in charge of the patient. Physical examination of live births is performed by physicians, mainly pediatricians. In case of *in utero* fetal death, spontaneous abortion, or therapeutic abortion, physical examination is performed by fetopathologists. In these cases, physicians are asked to send hospital discharge reports for precise description. Major malformations are defined in accordance with EUROCAT classification[4] (European Registry of Congenital Anomalies and Twins).

In our case series, the main interest was the presence of major congenital malformations in children or fetuses. Pregnant women whose healthcare providers contacted the CRAT from 1997 to 2009 because of paternal MTX exposure at the time of conception (or stopped within the 3 months

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before conception, i.e., within the spermatic cycle following the end of MTX) were included in the exposed group. Only prospective cases were taken into account (i.e., cases in which the physician calls the center while unaware of the pregnancy outcome). Retrospective cases (calls after detection of an adverse pregnancy outcome by prenatal diagnosis or after birth) are excluded from analysis. Only descriptive statistics are applied.

RESULTS

From 1997 to 2009, 42 pregnancies conceived by 40 fathers treated with MTX were reported to our center. The patients' mean age at conception was 38 years (range 30–52) and 31 years (range 19–41) for their female partner. The mean gestational age at call was 10.6 ± 5 weeks of gestation (i.e., after last menstrual period).

Indications for paternal MTX treatment are presented in Table 1. Twenty-three men were treated for an inflammatory disease [54.8%; mainly for rheumatic diseases (n = 18)], 9 for psoriasis (21.4%), 8 for a malignant disease (19.0%), and 2 for miscellaneous contexts.

In 10 cases (23.8%), MTX was associated with use of other drugs (infliximab, lamotrigine, hydroxychloroquine, azathioprine, tretinoin, acitretin, etanercept, vincristine, prednisone, and mercaptopurine). In 32 cases, MTX was the only medication.

Because of the different diseases involved, the MTX weekly dosages vary from 7.5 mg to 30 mg. This information is available for 34 cases (Figure 1). The median dose was 15 mg/week; weekly doses were generally ≤ 15 mg, and higher doses were not restricted to malignant diseases.

The 8 unknown dosages correspond to patients treated for leukemia (2), ankylosing spondylitis (1), psoriasis (2), lymphoma (1), and rheumatoid arthritis (RA; 2).

Length of treatment. Conceptions occurred while fathers were treated with MTX (n = 39) or in 3 cases during the 3 months following MTX cessation (respectively 2 weeks, 1 month, and 2 months after MTX had been stopped).

Duration of treatment once pregnancy was diagnosed is available in 31 cases. Paternal MTX was discontinued during the first trimester for 5 pregnancies (11.9%) and maintained until the end of the pregnancy for 23 (54.8%). We are aware of 3 patients who used condoms with their pregnant partner.

Outcomes. Pregnancy outcomes include 3 spontaneous abortions, 3 voluntary abortions, and 36 live births. For calculation of outcomes, elective terminations of pregnancies were excluded (Table 1).

The mean gestational age at birth for the 34 babies for which information is available was 39.2 ± 1.1 weeks. Preterm birth occurred in only 1 patient (36 weeks).

The mean birth weight (35 children), height (21 children), and head circumference (16 children) were 3393 ± 407 g, 49.3 ± 2.5 cm, and 34.6 ± 1.7 cm, respectively. The sex ratio was 1.9. The Apgar score at 1 minute was 9.06 (range 6–10; 27 children) and at 5 minutes it was 10 (23 children).

Among the 36 live births, no congenital malformation is reported. No fetopathological examination was performed for the 3 spontaneous and the 3 induced abortions. Within the 3 spontaneous abortions, no specific factor such as the type of the disease or the daily dose of MTX was notable.

The voluntary abortions were not done because of the prenatal diagnosis of fetal malformations. All were done for personal reasons. Because of maternal age, amniocenteses were performed in 6 pregnancies at risk for Down syndrome, and no chromosomal abnormality was reported.

DISCUSSION

To our knowledge, this is the largest prospective series of pregnancies (n = 42) in which the father was being treated with MTX at the time of conception.

No congenital abnormality was observed in this series in

Table 1. Outcomes of pregnancies in which fathers were under methotrexate treatment, and characteristics of that treatment.

Indications	Pregnancy During Male Treatment, n	Dose, mg/wk	Treatment Maintained Until End of Pregnancy, n	Other Treatments, n	Outcomes*
Rheumatoid arthritis	10	7.5–20	5	Prednisone (1), hydroxychloroquine (1), etanercept (1)	9 normal infants
Psoriasis	9	7.5–30	7	Acitretin (1)	7 normal infants, 1 SA
Ankylosing spondylitis	7	7.5–15	4	Infliximab (1)	6 normal infants
Leukemia	6	10–30	4	Mercaptopurine (4), tretinoin (1), vincristine (1)	4 normal infants, 2 SA
Crohn's disease	2	25	4		2 normal infants
Adrenal tumor	2	15	2		2 normal infants
Multiple sclerosis	2	12, 5–20	2		2 normal infants
Lymphomatoid papulosis	2	10–15	2		2 normal infants
Still's disease	1	20		Azathioprine (1)	1 normal infant
Sarcoidosis	1	7.5	1	Prednisone (1), lamotrigine (1)	1 normal infant
Total	42	7.5–30	31/42		36 normal infants (92.3%) 3 SA (7.7%)

* 3 voluntary abortions excluded from outcome calculations. SA: spontaneous abortion.

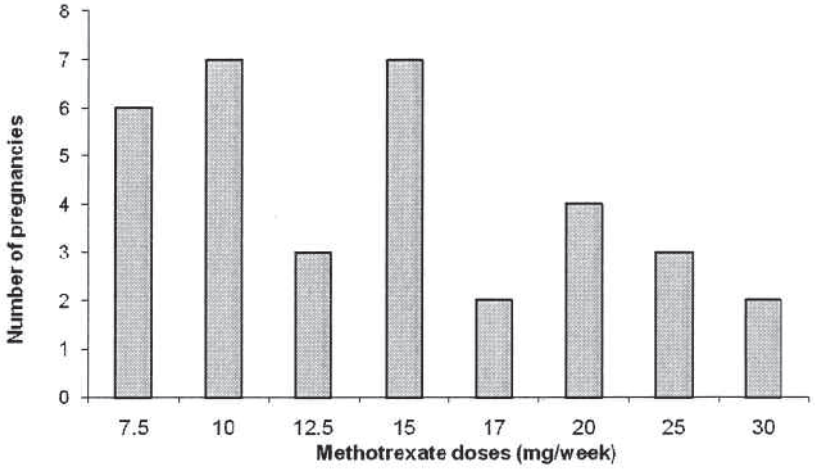

Figure 1. Methotrexate weekly dosage distribution.

which all fathers took MTX at the time of conception or stopped MTX within 3 months before conception.

Twenty-three pregnancies conceived while the father was being treated with MTX, mainly for rheumatic disease, have been reported (Table 2)[5,6,7,8,9,10,11]. Three out of 23 were reported after a paternal exposure to MTX for leukemia[12,13,14]. The outcomes include 19 normal children, 2 spontaneous abortions, and 2 children with malformations: an atrophy of one hand and a small fistula beneath the ear in one child, and an unspecified anomaly of the toes in another. The malformations were observed among 10 pregnancies in which the father was being treated for rheumatic diseases; in both cases, fathers were concomitantly treated with etanercept at the time of conception[7]. These first clinical results do not provide any evidence of an increased incidence of congenital abnormalities in children. Our results are similar to previous findings regarding diseases, dosages, and pregnancy outcomes.

As for other antineoplasic drugs (because of their teratogenic and genotoxic properties), paternal exposure to MTX

Table 2. Review of literature on pregnancy outcomes after paternal methotrexate exposure.

Study	Indication	Pregnancy During Male Treatment, n	Dose, mg/wk	Other Treatments	Outcomes	Malformation
Frank[8]	Psoriasis	2	25		2 normal infants	
Hinkes[13]	Leukemia	1	Unknown	Mercaptopurine, cyclophosphamide, prednisone	1 normal infant	
Kroner[14]	Acute lymphoblastic leukemia	2	25	Mercaptopurine	1 normal infant, 1 SA	
Weinstein[10]	Psoriasis	2	25	Mercaptopurine	2 normal infants	
Matthews[12]	Leukemia	1	Unknown	Daunorubicin, cytarabine, thioguanine	1 normal infant	
Perry[9]	Reiter's syndrome	1	25		1 normal infant	
Griggs[5]	Crohn's disease	1	25		1 normal infant	
Ostensen[7]	Rheumatic disease	10	Unknown	Etanercept (2 patients)	7 normal infants, 2 infants with malformation, 1 SA	Atrophy of one hand + small fistula beneath the ear Anomalies of the toes (type not specified)
Paschou[11]	Ankylosing spondylitis	2	Unknown	Infliximab	2 normal infants	
Lamboglia[6]	Crohn's disease	1	10	Infliximab	1 normal infant	
Total		23			19 normal infants (82.6%) 2 infants with malformation, 2 SA (8.7%)	

SA: spontaneous abortion.

at the time of conception raises 2 main questions. The first is the theoretical teratogenic effect on the embryo if the drug is present in the seminal fluid and is able to cross the vaginal mucosa in sufficient amount after sexual intercourse with a pregnant woman.

Investigators have measured MTX in testicular tissues after parenteral administration in animal models: concentrations were 2-fold to 4-fold lower in testicular interstitial fluid and 18-fold to 50-fold lower in seminiferous tubules, compared to plasma levels[15,16]. No measure of MTX in human seminal fluid is available, but on the basis of experimental results, it seems highly unlikely that this could be of any concern in treated patients, even with high weekly dosages. Nevertheless, because of a lack of documented information, condoms may be proposed as a precautionary measure to MTX-treated patients in case of sexual intercourse with a pregnant partner.

The second question is related to the possible genotoxic effect on sperm chromosomes induced by the mutagenic effects of MTX during the different maturation stages of spermatogenesis and leading to potentially abnormal effects on the offspring. MTX has been shown to induce micronuclei formation upon multiple doses in rats[17] and to increase chromosomal damage in bone marrow cells of treated patients[18,19]. Because of its biological mechanism of action, MTX is theoretically susceptible to induce sperm chromosomal abnormalities, potentially leading to abnormal pregnancy outcomes (i.e., fetal deaths and/or congenital abnormalities) if conception occurs during treatment or < 3 months after completion (i.e., one spermatogenic cycle).

This question is frequently raised among men exposed to antimitotic drugs in general. Epidemiological studies have failed to demonstrate any increased risk of malformations, genetic diseases, or childhood concerns in children of longterm cancer survivors who conceived a long time (several months and mostly several years) after the end of their cytotoxic treatments[20,21]. The remaining pending question is to clarify the consequences of chromosomal injuries induced in germ cells at the time of conception, when sperm DNA repair mechanisms are no more effective than in the earlier phases of sperm maturation.

It is well documented that during the entire period of cancer treatments (e.g., chemotherapy and/or radiotherapy) and a time interval of 18–24 months after the end of treatment, the rate of sperm DNA damage is increased compared to pretreatment values. This leads to enhanced structural and numerical chromosomal abnormalities, as well as DNA integrity damage in spermatozoa[22]. This is of particular concern if a conception occurs during this time interval, leading to possible transmission of unrepaired chromosomal and DNA damage to the conceptus. Observations of such genetic sperm damage have been described for testis cancers and lymphoma treatments, usually treated by multidrug chemotherapies containing alkylating and nonalkylating agents[22]. Extrapolation of these results to MTX is the key point of our study, as concerns about such possible consequences may lead to unnecessary actions such as pregnancy interruptions. Nonclinical and clinical results do not support similar fears for MTX. If there is evidence that MTX induces chromosomal damage to animal somatic and human bone marrow cells and interferes with some of the late stages of the spermatogenic cycle, namely spermiogenesis[23], no significant chromosomal breakage has been found in sperm of 4 male patients treated with low-dose MTX for RA[24]. Moreover, while no fetal karyotype was performed in the 23 published case reports, among the 6 amniocenteses performed in our study, no chromosomal abnormality was noted. While reassuring, this small number precludes any definitive conclusion regarding the occurrence of chromosomal aberrations in the children of fathers treated with MTX, and hindsight followup is too short to detect a longterm effect on children.

Therefore, amniocentesis should be proposed on a case-by-case basis, taking into account the risks and limits of the examination and other familial factors such as maternal age.

Our study follows the largest series of prospective pregnancies in which the father was an MTX-treated patient. Among 36 live births, no congenital malformation was observed after paternal exposure to low-dose MTX. Among those births, 6 amniocenteses were normal.

Although this is the largest published case series concerning paternal MTX exposure, our case series remains limited by its small size. Further studies are needed, especially for paternal exposure to high-dose MTX.

Our results confirm the previous results on small series or case reports. Moreover, the pregnancy outcomes remain similar in our group, despite a great variability among paternal indications.

Nevertheless, because of the mutagenic potential of MTX and the lack of information on its presence in seminal fluid, it seems wise, if possible, to stop paternal MTX treatment 3 months before conception and to use condoms during sexual intercourse with a pregnant woman.

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